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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,197	02/22/2005	Nobuhiko Fushimi	Q86306	7757

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EXAMINER
OLSON, ERIC

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,197	FUSHIMI ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,18-31,35-37 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-15,18-31 and 40* is/are allowed.

6)☒ Claim(s) *35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted July 3, 2008 wherein claims 19-26 and 29-37 are amended and claims 16, 17, 32-34, 38, and 39 are cancelled. This application is a national stage application of PCT/JP03/10551, filed August 21, 2003, which claims priority to foreign applications JP2002-244381, filed August 23, 2002, and JP2002-324076, filed November 7, 2002.

Claims 1-15, 18-31, 35-37, and 40 are pending in this application.

Claims 1-15, 18-31, 35-37, and 40 as amended are examined on the merits herein.

Applicant's amendment, submitted July 3, 2008, with respect to the rejection of instant claims 32-34, 38, and 39 under 35 USC 112, second paragraph for claiming a process without any steps, has been fully considered and found to be persuasive to remove the rejection as the rejected claims have been cancelled. Therefore the rejection is withdrawn.

Applicant's amendment, submitted July 3, 2008, with respect to the rejection of instant claims 16, 17, and 19-39 under 35 USC 112, first paragraph for lacking enablement for prodrugs, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to no longer include prodrugs. Therefore the rejection is withdrawn.

Applicant's amendment, submitted July 3, 2008, with respect to the rejection of instant claims 22, 23, 25, 26, 29, 31, 32, 34, 36, and 38 under 35 USC 112, first paragraph for lacking enablement for preventative methods, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to no longer include preventative methods. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising known antidiabetic drugs such as insulin, glyburide, repaglinide, metformin, rosiglitazone, acarbose, and similar drugs, does not reasonably provide enablement for compositions comprising any of the broad classes of second active agents recited in the claims. (e.g. "insulin sensitivity enhancer," "glucose absorption inhibitor," "insulin secretion enhancer," "SGLT2 inhibitor," etc.) The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a composition of two or more pharmaceutical active agents. In order to be enabled, one skilled in the art must be able to obtain all of the possible ingredients readily without undue experimentation.

The state of the prior art: Various substances are known to be useful for controlling blood sugar in diabetes, for example insulin, compounds such as sulfonylureas that stimulate insulin production, or compounds such as acarbose that inhibit glucose absorption. Additionally, certain other pharmaceutical agents, such as cholesterol-lowering HMG-CoA inhibitors or blood pressure lowering diuretics, are known to be useful for managing complications of diabetes. However, these classes of drugs are open-ended and defined by functional language. The prior art does not disclose any general method for discovering all possible compounds with a particular activity, (e.g. all compounds that stimulate insulin production) and certainly does not provide a complete, exhaustive list of all such compounds. Also note that the prior art gives no reason to expect all compounds of a given biological function to share a related core structure.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The diversity of possible chemical substances is very broad, And only a tiny fraction of this diversity has been characterized in the art. Because many different structures can produce the same function *in vivo*, it is not possible to predict beforehand which compounds will possess a given therapeutic activity.

Furthermore, while many compounds can be produced by chemical synthesis, this process is not completely predictable when applied to every possible compound that one skilled in the art would want to make. The synthesis of a novel organic compound is a complex process involving multiple unpredictable synthetic transformations. Often unforeseen difficulties arise during the synthesis of a novel structure that can only be surmounted by original research and trial and error. Furthermore, the steps necessary to synthesize a compound depend not on its biological function but rather on its structure. Therefore one skilled in the art would find the synthesis of broad classes of structurally unrelated molecules to be highly unpredictable.

The Breadth of the claims: The claimed invention is very broad, including any substance, whether it be an organic small molecule, a polysaccharide, a polypeptide, an oligonucleotide, a viral vector, or any other therapeutic agent that would produce the claimed therapeutic effect.

The amount of direction or guidance presented: Applicant's specification is directed toward certain glycosyloxy-pyrazoles that produce a hypoglycemic effect *in vivo* and are therefore useful for treating diabetes and related conditions. These compounds are shown to work by inhibiting the sodium-dependent glucose cotransporter. While guidance is given for assays that could be used to test novel compounds for SGLT inhibition, no guidance is given for how to discover antidiabetic compounds that function by any other mechanism, for example by lowering cholesterol.

The presence or absence of working examples: No working examples of any actual therapeutic method are shown.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of broad ranges of novel compounds. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of second therapeutic agents beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful in any of the categories claimed. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have any of the recited antidiabetic activities. For most compounds, it is unknown whether they are or are not useful as second active agents. Gathering this data for every compound known to man would involve *in vitro*

screening of an enormous diversity of chemical compounds for a wide variety of therapeutic activities, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential second active agents, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible adenosine A_{2A} antagonist, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of second agents claimed.

Genentech, 108 F.3d at 1366, sates that, “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion.” And “patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all of the possible second agents falling within the categories of claims 35-37.

Response to Argument: Applicant's argument, submitted July 3, 2008, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the classes of agents remaining in the claims after the amendment are limited to those that are well known by those skilled in the art. However, as discussed in the body of the rejection, several of the classes of agents (i.e. insulin sensitivity enhancer, SGLT2 inhibitor, insulin secretion enhancer) are still broad functionally defined classes of active agent that one skilled in the art would not be able to make and use without an undue and unpredictable experimental burden. Therefore the rejection is maintained and made **FINAL**.

Conclusion

Claims 35-37 are rejected. Claims 1-15, 18-31, and 40 are seen to be allowable. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
9/2/2008

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623